UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/431,594	11/01/1999	JEFFERY J. WHEELER	16303-002430	8936

500 7590 03/07/2006

SEED INTELLECTUAL PROPERTY LAW GROUP PLLC
701 FIFTH AVE
SUITE 6300
SEATTLE, WA 98104-7092

EXAMINER	
ZARA, JANE J	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 03/07/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/431,594	WHEELER ET AL.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *42,44-46 and 48-79* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *42,44-46 and 48-79* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office action is in response to the communication filed 12-21-05.

Claims 42, 44-46, 48-79 are pending in the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The unexecuted declaration under 37 CFR 1.132 filed 12-21-05 is insufficient to overcome the rejection of claims 42, 44-61, 62-75 based upon 102 and 103 as set forth in the last Office actions 8-9-01, 5-16-02, 3-25-03, 12-15-03, 9-30-04 and 6-14-05 and for the reasons set forth below.

Response to Arguments and Amendments

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

Maintained Rejections

Claims 42, 44-46, 48-61, 63-77 and 79 are rejected under 35 U.S.C. 102(e) as being anticipated by Choi et al for the reasons of record set forth in the Office actions mailed 8-9-01, 5-16-02, 3-25-03, 12-15-03, 9-30-04 and 6-14-05.

Claims 42, 44-46, 48-61, 63-64, 67-77 and 79 are rejected under 35 U.S.C. 102(e) as being anticipated by Holland et al for the reasons of record set forth in the Office actions mailed 12-5-03, 9-30-04 and 6-14-05.

Claim 62, 75-77 and 79 are rejected under 35 U.S.C. 103(a) as being unpatentable over Choi et al for the reasons of record set forth in the Office actions mailed 12-15-03, 9-30-04 and 6-14-05 and for the reasons of record set forth below.

Applicant's arguments and the unexecuted declaration filed 12-21-05 have been fully considered but they are not persuasive. Applicant argues that the instant claims are neither anticipated nor rendered obvious by Choi or Holland because neither Choi nor Holland exemplify a working embodiment of the claimed invention. Applicant also argues that the teachings of Choi and Holland result in an inoperative nucleic acid-lipid composition because the methods described by Choi or Holland result in extraordinarily inefficient encapsulation of nucleic acids compared to the instant methods claimed. It is noted that the instant claims are compositions and not methods. The limitations of the methods are therefore not

It is again noted that the instant invention is drawn to compositions, not methods. Limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed.Cir. 1993). The compositions of the instant invention comprise chemical compositions as disclosed by Choi and Holland, and therefore cannot have mutually exclusive properties. (See *In re Spada*, 911 F2d 705, 709, 15 USPQ2d1655, 1658 (Fed. Cir. 1990). The methods utilized by Choi and Holland yield compositions as claimed, albeit inefficiently, as asserted by applicant.

Choi teaches compositions comprising bioactive agents encapsulated in lipid compositions comprising DOCAC, DOPE and conjugated lipids including PEG-ceramide (where ceramide has 8, 12 or 20 carbon) or PEG-phosphatidylethanolamine. Choi and

Holland teach the inhibition of aggregation with the conjugated lipids claimed. Choi, at claims 1, 4, 5, 16 and 17, disclose compositions comprising liposomal formulations that include "gene constructs" and "oligonucleotides" for therapeutic use, which liposomal compositions are explicitly used "for delivering bioactive agents to cells comprising encapsulating the agent in a liposome" (*e.g. see claims 6 and 27). Choi provides liposomal formulations for encapsulating bioactive agents, thereby increasing the circulating half-life of these delivery constructs in vivo (see e.g. columns 20-22, examples 7-10, delineating compositions and methods for entrapping bioactive agents and thereby increasing circulating time of the agents in serum. The entire focus of Choi addresses compositions and methods for encapsulating bioactive agents for increasing target cell delivery in an animal. The prior art compositions meet the structural limitations of the claimed compositions. The bioactive agents in these compositions anticipated by Choi include oligonucleotides intended to block production of a protein with a target cell (see col. 17, line 66-col. 18, line 24 of Choi. See also claims 4, 5, 16 and 17 of Choi). The genus of nucleic acids used to block protein expression includes ribozymes, antisense oligonucleotides (e.g. DNA-RNA hybrids), all of which were well known in the art at the time the instant invention was made.

Choi reviews previously existing liposomal formulations traditionally used to deliver nucleic acids. See column 18 of Choi: "The efficiency of this transfection has often been less than desired, for various reasons. One is the tendency for cationic lipids complexed to nucleic acids to form unsatisfactory carriers. These carriers are improved by the inclusion of PEG lipids." After reviewing the existing liposomal

compositions traditionally used for nucleic acid, and their shortcomings, Choi explicitly state: "The invention will be better understood by reference to the following examples, which are intended to illustrate aspects of the invention..." (col.18, lines 24-26), after which follows the encapsulation compositions and methods for increasing the circulation time/plasma stability of bioactive agents (e.g. examples 1-10).

Holland discloses compositions comprising a lipid selected from phosphatidylethanolamines (e.g. DOPE, col. 4), phosphatidylserines, ceramides, glycolipids and mixtures thereof, and further comprising a polyethyleneglycol-ceramide conjugate reversibly associated with the lipid, and whereby a PEG-ceramide conjugate ranges from –05 to 50 mole percent, and which compositions further comprise a cationic lipid selected from e.g. DOTMA or DDAC, and which compositions comprise amphipathic particles between –05-.45 microns, and which PEG-ceramides comprise saturated or unsaturated fatty acid carbon chains between two and 31 carbons in length (see col. 7-8). Choi teaches compositions for the delivery of bioactive agents, including nucleic acids, comprising DODAC, DOPEP and PEG-ceramide (col. 2-3, col. 24-26), and which compositions comprise conjugated PEG-ceramide or PEG-phosphatidylethanolamine, which ceramide has 8, 14 or 20 carbons (see Table 11), and which amphipathic particles are between 89-103 nm, and comprise 5-10% PEG-ceramide, and which conjugated lipid inhibits aggregation of lipid containing, amphipathic particles.

Claims 42, 44-46, 48-79 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for the reasons of record set forth in the Office action mailed 6-14-05.

Claim 78 is drawn to double stranded RNA containing nucleic acid lipid particles. There is no support for such double stranded RNA molecules in the instant disclosure. This is a new matter rejection. Applicant is encouraged to specifically point out the support for this claim in the original disclosure.

Applicant's arguments filed 12-21-05 have been fully considered but they are not persuasive. Applicant argues that the broadly claimed genus is adequately described because it is the general nature and combination of components that achieves the desired result and not any specific species of component. Applicant also argues that a representative number of species of cationic lipids have been taught in the instant specification, providing adequate support for the broadly claimed genus.

The claims are drawn to compositions comprising nucleic acid-lipid particles of one or mixture of one or more cationic lipids, a conjugated lipids that inhibit aggregation of particles, and which compositions optionally further comprise additional, non-cationic lipids, and whereby the nucleic acids are encapsulated in the lipids and are resistant to nuclease degradation and the particles are inhibited from aggregating.

Contrary to Applicant's assertions, the disclosure of compositions comprising various stoichiometries of DOPE, DDAB and/or DODAC in combination with either PEG-Cer C8 or PEG-Cer-C14 are not representative of the broad genus comprising one or mixture of one or more of any cationic lipids, any conjugated lipids that inhibit

aggregation of particles, and which compositions optionally further comprise any additional, non-cationic lipids, and whereby the nucleic acids are encapsulated in the lipids and are resistant to nuclease degradation and the particles are inhibited from aggregating. The genus claimed embraces thousands of cationic, non-cationic and conjugated lipids and mixtures thereof. One of skill would reasonably conclude that the instant disclosure does not adequately describe the very broad genus claimed.

New Rejections

Claims 69, 70, 72-75 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for in vitro transfection of target cells with nucleic acids using lipid formulations particularly described in the examples delineated in the specification, does not reasonably provide enablement for methods of in vivo delivery and treatment effects provided for the broad genus of compositions claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to pharmaceutical compositions comprising nucleic acid-lipid particles of one or mixture of one or more cationic lipids, a conjugated lipids that inhibit aggregation of particles, and which compositions optionally further comprise additional, non-cationic lipids, and whereby the nucleic acids are encapsulated in the lipids and are resistant to nuclease degradation and the particles are inhibited from aggregating.

The state of the prior art and the predictability or unpredictability of the art. Branch and Crooke teach that the in vivo (whole organism) application of nucleic acid molecules is a highly unpredictable endeavor due to target accessibility and delivery issues. Crooke also points out that cell culture examples are generally not predictive of *in vivo* inhibition of target molecules. (See entire text of A. Branch, Trends in Biochem. Sci., 23, 45-50, 1998; and S. Crooke, Antisense Res. & Application, Chapter 1, pages 1-50, ed. by S. Crooke, Springer-Verlag, especially pages 34-36).

Peracchi cites stability and delivery obstacles that need to be overcome in achieving desired in vivo efficacy using nucleic acid molecules for expressing a polypeptide and for inhibiting the expression of a polypeptide using antisense oligonucleotides: "A crucial limit of ribozymes in particular, and of oligonucleotide-based drugs in general, lies in their intrinsically low ability to cross biological membranes, and therefore to enter the cells where they are supposed to operate...cellular uptake following systemic administration appears to require more sophisticated formulations... the establishment of delivery systems that mediate efficient cellular uptake and sustained release... remains one of the major hurdles in the field." ((See Peracchi et al, Rev. Med. Virol., 14, pages 47-64, 2004, abstract on page 47 and text on page 51).

Cellular uptake by appropriate target cells is a rate limiting step that has yet to be overcome in achieving predictable clinical efficacy. Both Chirila et al and Agrawal et al point to the current limitations which exist in our understanding of the cellular uptake of small molecules in vitro and in vivo (see Agrawal et al, Molecular Med. Today, Vol. 6, pages 72-81, 2000, especially at pages 79-80; see Chirila et al, Biomaterials, Vol. 23,

pages 321-342, 2002, especially pages 326-327 for a general review of the important and inordinately difficult challenges of the delivery of therapeutic molecules to target cells).

The amount of direction or guidance presented in the specification AND the presence or absence of working examples. The specification discloses the in vitro transfection of target cells with several lipid containing compositions comprising encapsulated nucleic acids. Applicants have not provided adequate guidance in the specification toward a method of providing any treatment effects using the broadly claimed lipid compositions. One skilled in the art would not accept on its face the examples given in the specification of the in vitro transfection of target cells with particularly described lipid containing compositions as being correlative or representative of the ability to deliver nucleic acids to target cells in vivo using the broadly claimed genus of lipid containing compositions and further whereby treatment effects are provided, as instantly claimed. There is a lack of guidance in the specification and an unpredictability associated with the successful targeting and delivery of nucleic acids or other molecules to appropriate target cells in an organism whereby treatment is obtained.

The breadth of the claims and the quantity of experimentation required. The claims are broadly drawn to pharmaceutical compositions comprising nucleic acid-lipid particles of one or mixture of one or more cationic lipids, a conjugated lipids that inhibit aggregation of particles, and which compositions optionally further comprise additional, non-cationic lipids, and whereby the nucleic acids are encapsulated in the

lipids and are resistant to nuclease degradation and the particles are inhibited from aggregating.

The quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of a representative number of species of the broad genus of lipid compositions claimed, whereby adequate delivery of nucleic acids occurs in vivo and treatment effects are provided in an animal. Other experimentation required to practice the invention claimed includes determining accessible target sites, modes of delivery and specifically described formulations to target appropriate cells and /or tissues in an organism, whereby the compounds and compositions claimed are effectively delivered in adequate quantities to the target cells, and treatment effects are provided. Since the specification fails to provide sufficient guidance for the methods or the broad genus of compositions claimed, and since determination of these factors is highly unpredictable, it would require undue experimentation to practice the invention over the scope claimed.

Double Patenting

Claims 42, 44-46, 48-68, 76, 77, 79 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 7, 13, 23 and 29 of U.S. Patent No. 5,976,567. Although the conflicting claims are not identical, they are not patentably distinct from each other because both claimed inventions are drawn to compositions comprising nucleic acid-lipid particles of one or mixture of one or more cationic lipids, a conjugated lipids that inhibit aggregation of particles, and which

compositions optionally further comprise additional, non-cationic lipids, and whereby the nucleic acids are encapsulated in the lipids and are resistant to nuclease degradation and the particles are inhibited from aggregating.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. 1.6(d)). The official fax telephone number for the Group is **571-273-8300**. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(571) 272-0765.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang, can be reached on (571) 272-0811. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (571) 272-0564. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jane Zara
3-3-06

Jane Zara
TC1600

JANE ZARA, PH.D.
PRIMARY EXAMINER